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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Substituted Arylureas

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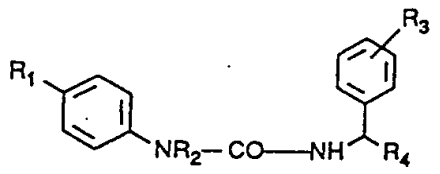
(57) 13 Claims

The invention relates to substituted arylureas, a process for their preparation and their use in medicaments, in particular for the treatment of arteriosclerosis and restenosis.

The present invention relates to substituted arylureas of the general formula (I)



(I)

in which

R^1 represents a radical of the formula $-CH_2-A$ or $-O-CH_2-D$,

in which

A and D are identical or different and denote hydrogen or a 5- to 7-membered, saturated or unsaturated heterocycle having up to 3 nitrogen atoms, to which a phenyl or pyridyl ring is optionally fuzed, and where in the case of an N-containing ring the bonding to the methylene group can also take place via

the nitrogen function, and where the cycles are optionally substituted up to 3 times by identical or different straight-chain or branched alkyl, alkoxy or alkoxycarbonyl in each case having up to 8 carbon atoms, cycloalkyl having 3 to 6 carbon atoms, phenyl, hydroxyl, carboxyl or halogen,

R^2 represents cycloalkyl having 3 to 7 carbon atoms or straight-chain or branched alkyl having up to 8 carbon atoms,

R^3 represents hydrogen or halogen,

and

R^4 represents carboxyl or straight-chain or branched alkoxycarbonyl having up to 8 carbon atoms, or
represents straight-chain or branched alkyl having up to 6 carbon atoms, which is substituted by hydroxyl, or
represents a group of the formula $-CO-NR^5R^6$,

in which

R^5 and R^6 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,

and their salts.

The substituted arylureas according to the invention can also be present in the form of their salts. In general, salts with organic or inorganic bases or acids may be mentioned here.

In the context of the present invention physiologically acceptable salts are preferred. Physiologically acceptable salts of the compounds according to the invention can be salts of the substances according to the invention with mineral acids, carboxylic acids or sulphonic acids. Particularly preferred salts are e.g. those with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid.

Physiologically acceptable salts can also be metal or ammonium salts of the compounds according to the invention which have a free carboxyl group. Particularly preferred salts are e.g. sodium, potassium, magnesium or calcium salts, and also ammonium salts which are derived from ammonia, or organic amines, such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine, ethylenediamine or 2-phenylethylamine.

The compounds according to the invention can also exist in stereoisomeric forms which either behave as image and

mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the enantiomers or diastereomers or their respective mixtures. Like the diastereomers, the racemates can also be separated into the stereoisomerically uniform constituents in a known manner.

Heterocycle in general represents a 5- to 7-membered, preferably 5- to 6-membered, saturated or unsaturated ring which as heteroatoms can contain up to 3 nitrogen atoms and to which a phenyl or pyridyl ring can optionally also be fused. Benzo-fused 5-membered heterocycles and quinolines are preferred. Examples which may be mentioned are: pyrrolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, imidazolyl, pyrrolidinyl, piperidinyl, piperazinyl, benzimidazolyl, 3H-imidazopyridyl, 1-indolyl, 3-indolyl or 2-quinolinyl. Benzimidazolyl, 3H-imidazopyridyl, 3-indolyl or 2-quinolinyl are particularly preferred.

Preferred compounds of the general formula (I) are those

in which

R^1 represents a radical of the formula $-CH_2-A$ or $-O-CH_2-D$,

in which

A and D are identical or different and denote

hydrogen, benzimidazolyl, 3H-imidazopyridyl, 3-indolyl or 2-quinolinyl, which are optionally substituted up to 2 times both in the phenyl and in the heterocyclic radical by identical or different straight-chain or branched alkyl, alkoxy or alkoxycarbonyl in each case having up to 6 carbon atoms, cyclopropyl, cyclopentyl, cyclohexyl, hydroxyl, phenyl, carboxyl, fluorine, chlorine or bromine,

R^2 represents cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl, or
represents straight-chain or branched alkyl having up to 6 carbon atoms,

R^3 represents hydrogen, fluorine, chlorine or bromine,

and

R^4 represents carboxyl or straight-chain or branched alkoxycarbonyl having up to 6 carbon atoms, or
represents straight-chain or branched alkyl having up to 4 carbon atoms, which is substituted by hydroxyl, or
represents a group of the formula $-CO-NR^5R^6$,

in which

R^5 and R^6 are identical or different and denote hydrogen or straight-chain or branched alkyl

having up to 4 carbon atoms,

and their salts.

Particularly preferred compounds of the general formula (I) are those

in which

R^1 represents a radical of the formula $-CH_2-A$ or $-O-CH_2-D$,

in which

A and D are identical or different and denote hydrogen, benzimidazolyl, 3H-imidazopyridyl, 3-indolyl or 2-quinolinyl, which are optionally substituted up to 2 times both in the phenyl and in the heterocyclic radical by identical or different straight-chain or branched alkyl, alkoxy or alkoxycarbonyl in each case having up to 5 carbon atoms, cyclopropyl, cyclopentyl, cyclohexyl, hydroxyl, phenyl or carboxyl,

R^2 represents cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl, or
represents straight-chain or branched alkyl having up to 4 carbon atoms,

R^3 represents hydrogen, fluorine, chlorine or bromine,

and

R^4 represents carboxyl or straight-chain or branched alkoxycarbonyl having up to 3 carbon atoms, or represents straight-chain or branched alkyl having up to 3 carbon atoms, which is substituted by hydroxyl, or represents a group of the formula $-CO-NR^5R^6$,

in which

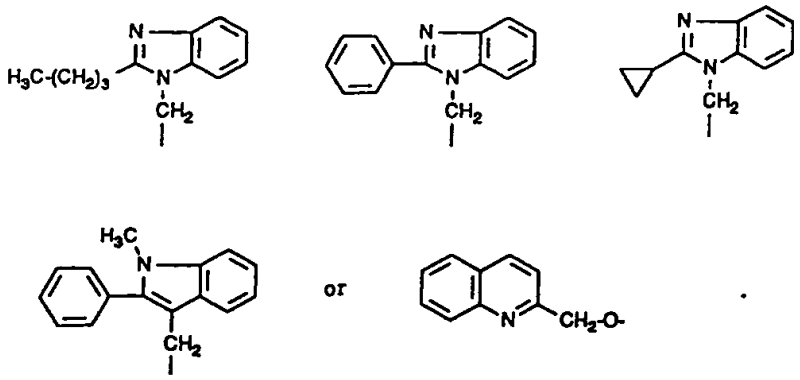
R^5 and R^6 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

and their salts.

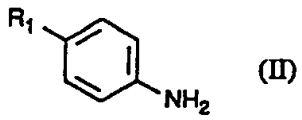
Very particularly preferred compounds of the general formula (I) are those

in which

R^1 represents hydrogen or the radical of the formula



A process for the preparation of the compounds of the general formula (I) according to the invention has additionally been found, characterized in that compounds of the general formula (II)



(II)

in which

R^1 has the meaning indicated above,

are first converted by reaction with compounds of the general formula (III)

$$R^2\text{-}L \qquad \text{(III)}$$

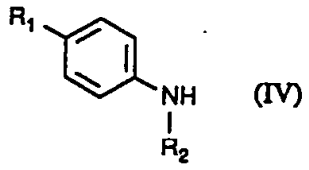
in which

R^2 has the meaning indicated above

and

L represents halogen, preferably bromine,

in inert solvents, in the presence of a base and under a protective gas atmosphere, to the compounds of the general formula (IV)

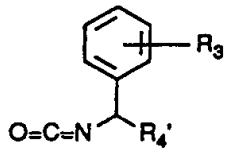


(IV)

in which

R^1 and R^2 have the meaning indicated above,

and in a second step the latter are reacted with compounds of the general formula (V)



(V)

in which

R^3 has the meaning indicated above

and

$R^{4'}$ represents straight-chain or branched alkoxycarbonyl having up to 8 carbon atoms,

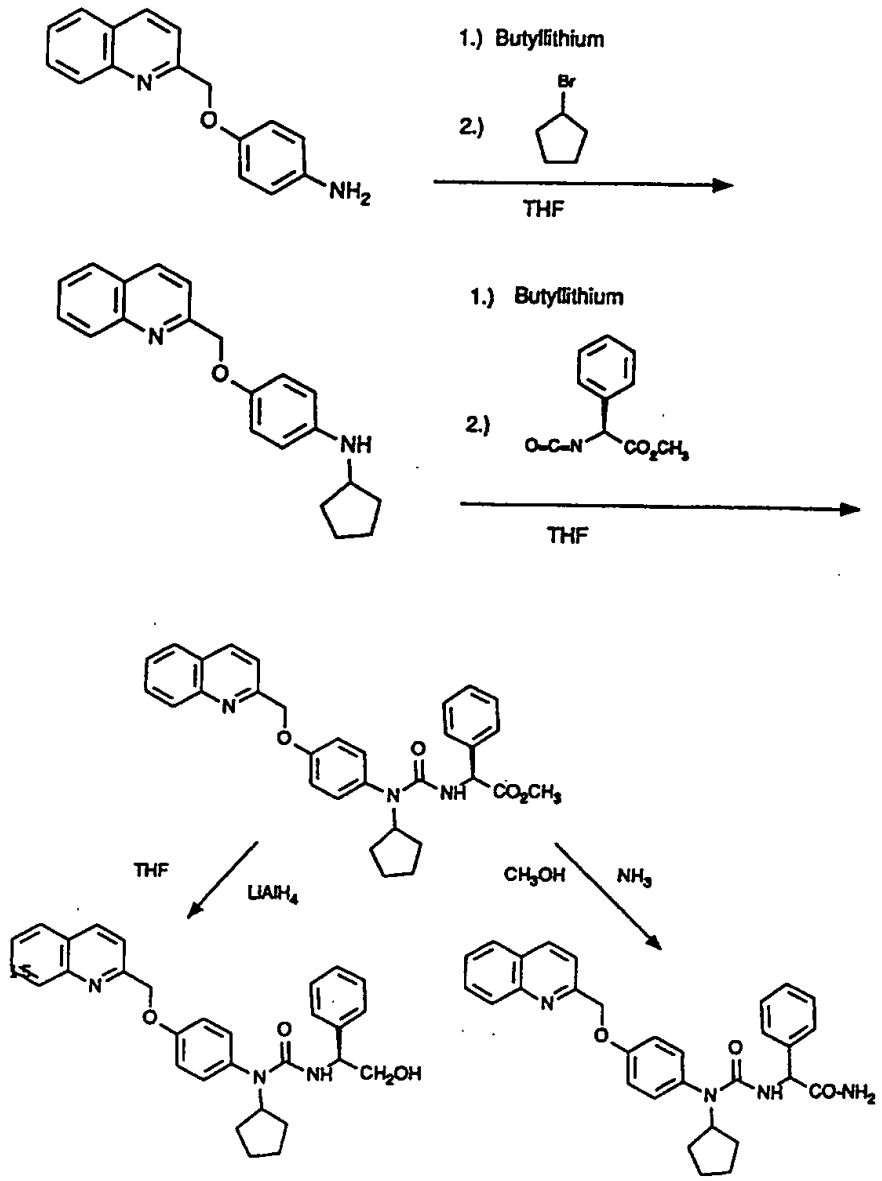
in inert solvents, if appropriate in the presence of a base and under a protective gas atmosphere,

and in the case of the acids $R^4 = CO_2H$, the esters are hydrolysed,

in the case of the alkylhydroxy compounds, the esters are reduced according to customary conditions,

and in the case of the amides, the esters or acids are reacted either with ammonia ($R^4 = CO\text{-}NH_2$) or with amines, if appropriate after prior activation of the carboxylic acid function.

The process according to the invention can be illustrated by way of example by the following reaction scheme:


1.) Butyllithium
2.)
Br
THF
1.) Butyllithium
2.)
O=C=N
CO2CH3
THF
THF
LiAlH4
CH3OH
NH3
CH2OH
CO-NH2

For the reactions with the compounds of the general formulae (II) and (IV), inert solvents which do not change under the reaction conditions are in general suitable. These preferably include ethers such as, for example, dioxane, tetrahydrofuran or diethyl ether, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, dimethylformamide or acetonitrile. It is also possible to employ mixtures of the solvents. Tetrahydrofuran is preferred.

Suitable bases for these reactions are alkali metal or alkaline earth metal hydroxides such as, for example, sodium hydroxide, potassium hydroxide, lithium hydroxide or barium hydroxide, alkali metal carbonates such as sodium carbonate or potassium carbonate, alkaline earth metal carbonates such as calcium carbonate or alkali metal or alkaline earth metal alkoxides or amides such as sodium methoxide or potassium methoxide, sodium ethoxide or potassium ethoxide or potassium tert-butoxide or lithium diisopropylamide (LDA), or n-butyllithium, or organic amines (trialkyl(C_1-C_6)amines) such as triethylamine, or heterocycles such as 1,4-diazabicyclo-[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, N,N-dimethylaminopyridine (DMAP), methylpiperidine or morpholine. It is also possible to employ alkali metals as bases, such as sodium, or their hydrides such as sodium hydride. Triethylamine, lithium hydroxide, DBU, N,N-dimethylaminopyridine and n-butyllithium are preferred.

In general, the base is employed in an amount from 0.05 mol to 10 mol, preferably from 1 mol to 2 mol, relative to 1 mol of the compound of the formula (II).

The process according to the invention is in general carried out in a temperature range from -30°C to +100°C, preferably from -10°C to +60°C.

The process according to the invention is in general carried out at normal pressure. However, it is also possible to carry out the process at elevated pressure or at reduced pressure (e.g. in a range from 0.5 to 5 bar).

Suitable bases for the hydrolysis are the customary inorganic bases. These preferably include alkali metal hydroxides or alkaline earth metal hydroxides such as, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide or barium hydroxide, or alkali metal carbonates such as sodium carbonate or potassium carbonate or sodium hydrogen carbonate, or alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide or potassium tert-butoxide. Lithium hydroxide, sodium hydroxide or potassium hydroxide is particularly preferably employed.

Suitable solvents for the hydrolysis are water or the organic solvents customary for hydrolysis. These preferably include alcohols such as methanol, ethanol, propanol, isopropanol or butanol, or ethers such as tetrahydrofuran or dioxane, or dimethylformamide, or

dimethyl sulphoxide. Dioxane-water mixtures are particularly preferably employed.

Hydrolysis can also be carried out using acids such as, for example, trifluoroacetic acid (TFA), acetic acid, hydrochloric acid, hydrobromic acid, methanesulphonic acid, sulphuric acid or perchloric acid, preferably using trifluoroacetic acid.

The hydrolysis is in general carried out in a temperature range from 0°C to +100°C, preferably from +20°C to +80°C.

In general the hydrolysis is carried out at normal pressure. However, it is also possible to work at reduced pressure or at elevated pressure (e.g. from 0.5 to 5 bar).

When carrying out the hydrolyis, the base is in general employed in an amount from 1 to 3 mol, preferably from 1 to 1.5 mol, relative to 1 mol of the ester. Molar amounts of the reactants are particularly preferably used.

When carrying out the reaction, the carboxylates of the compounds according to the invention are formed in the first step as intermediates which can be isolated. The acids according to the invention are obtained by treating the carboxylates with customary inorganic acids. These preferably include mineral acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid or phosphoric acid. It has proven advantageous in this

connection in the preperation of the carboxylic acids to acidify the basic reaction mixture from the hydrolysis in a second step without isolation of the carboxylates. The acids can then be isolated in a customary manner.

Amidation of the terminal esters (R^4 = $-CO-NR^5R^6$) is in general carried out in one of the abovementioned solvents, preferably in alcohols such as methanol, ethanol, propanol or isopropanol, or in ethers such as tetrahydrofuran or dioxane, or in mixtures of these, if appropriate with addition of water.

Amidation of the terminal esters may optionally proceed via the activated stage of the acid halides, which can be prepared from the corresponding acids by reaction with thionyl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus tribromide or oxalyl chloride.

Amidation of the terminal esters is in general carried out in a temperature range from -20°C to +80°C, preferably from -10°C to +30°C, and at normal pressure.

The base is employed in an amount from 0.5 mol to 10 mol, preferably from 1 mol to 5 mol, relative to 1 mol of the corresponding carboxylic acids or esters.

Acid-binding agents which can be employed for the amidation are alkali metal or alkaline earth metal carbonates such as sodium carbonate, potassium carbonate, alkali metal or alkaline earth metal hydroxides such as,

for example, sodium hydroxide or potassium hydroxide, or organic bases such as pyridine, triethylamine, N-methylpiperidine, or bicyclic amidines such as 1,5-diazobicyclo[4.3.0]non-5-ene (DBN), 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), dimethylaminopyridine, DABCO or N,N-dimethylaminopyridine. Potassium carbonate is preferred.

Suitable dehydrating reagents are carbodiimides such as, for example, diisopropylcarbodiimide, dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride or carbonyl compounds such as carbonyldiimidazole or 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium-3-sulphonate or propanephosphonic anhydride or isobutyl chloroformate or benzotriazolyloxy-tris-(dimethylamino)phosphonium hexafluorophosphate or diphenyl phosphoramidate or methanesulphonyl chloride, if appropriate in the presence of bases such as triethylamine or N-ethylmorpholine or N-methylpiperidine or dicyclohexylcarbodiimide, N-hydroxybenzotriazole or N-hydroxysuccinimide. N,N-Dicyclohexylcarbodiimide is preferred, if appropriate in the presence of triethylamine and N-hydroxybenzotriazole.

The acid-binding agents and dehydrating reagents are in general employed in an amount from 0.5 to 3 mol, preferably from 1 to 1.5 mol, relative to 1 mol of the corresponding carboxylic acids.

The reduction of alkoxycarbonyl compounds to the corresponding alcohols is in general carried out using hydrides, preferably using lithium aluminium hydride in inert solvents such as ethers, hydrocarbons or alcohols or their mixtures, preferably in ethers such as, for example, diethyl ether, tetrahydrofuran or dioxane, in a temperature range from -20°C to +150°C, preferably from 0°C to +40°C, at normal pressure.

The individual derivatization steps are in general carried out in a temperature range from -78°C to +80°C, preferably from -40°C to room temperature. It may be necessary to work under a protective gas atmosphere.

The reaction of the compounds of the general formula (IV) is carried out in one of the abovementioned solvents, such as, for example, tetrahydrofuran, dioxane, dimethylformamide or toluene. Tetrahydrofuran is particularly preferred.

A suitable base for this step is one of the abovementioned bases, preferably butyllithium, potassium carbonate or triethylamine.

In general, the base is employed in an amount from 0.05 to 10 mol, preferably from 1 mol to 2 mol, in each case relative to 1 mol of the compound of the formula (IV).

The process according to the invention is in general carried out in a temperature range from -78°C to +100°C,

preferably from -20°C to +80°C.

The compounds of the general formula (II) are known in some cases or are new and can be prepared, for example, by reacting either, as in the case of the methylenoxy-bridged products, the corresponding halogenomethylene compounds with p-nitrophenol, or, as in the case of the methylene-bridged products, the corresponding hetero-cycles with p-bromomethylnitrobenzene in one of the abovementioned solvents, preferably dimethylformamide or ethanol, in a temperature range from -78°C to +150°C, preferably at -20°C to +100°C,

and reducing in a second step, likewise in one of the abovementioned solvents, preferably tetrahydrofuran, according to customary reduction methods, such as e.g. by catalytic hydrogenation or by use of suitable reducing agents, preferably by use of titanium trichloride solution, under a pressure of 0.1 bar.

The compounds of the general formula (I) according to the invention show an unforeseeable, useful spectrum of pharmacological action.

The compounds of the general formula (I) according to the invention inhibit the proliferation of smooth muscle cells. They can therefore be employed for the treatment of arteriosclerosis and of restenosis.

Investigation of inhibition of the proliferation of smooth muscle cells by the compounds according to the invention

To determine the antiproliferative action of the compounds, smooth muscle cells are used which are obtained from the aortas of rats by the media explant technique [R. Ross, J. Cell. Biol. 50, 172, 1971]. The cells are inoculated into suitable culture dishes, as a rule 96-hole plates, and cultured at 37°C in 5 % CO_2 for 2-3 days in medium 199 with 7.5 % FCS and 7.5 % NCS, 2 mM L-glutamine and 15 mM HEPES, pH 7.4. The cells are then synchronized for 2-3 days by serum withdrawal and then stimulated into growth using serum or other factors. At the same time, test compounds are added. After 16-20 hours, 1 µCi of ^{3}H-thymidine is added and after a further 4 hours the incorporation of this substance into the TCA-precipitatable DNA of the cells is determined. For determination of the IC_{50} values, the active compound concentration is calculated which, on sequential dilution of the active compound, causes half the maximum inhibition of the thymidine incorporation produced by 10 % FCS.

The new active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, non-toxic, pharmaceutically suitable excipients or solvents. In this connection the therapeutically active compound

should in each case be present in a concentration of about 0.5 to 90 % by weight of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

The formulations are prepared, for example, by extending the active compounds with solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, where e.g. if water is used as a diluent, organic solvents can optionally be used as auxiliary solvents.

Administration is carried out in a customary manner, preferably orally or parenterally, in particular perlingually or intravenously.

For the case of parenteral administration, solutions of the active compound can be employed using suitable liquid excipient materials.

The invention also extends to a commercial package containing a compound of the invention, together with instructions for its use for inhibiting the proliferation of smooth muscle cells or for the treatment of arteriosclerosis or restenosis.

In general, it has proven advantageous in the case of intravenous administration to administer amounts of about 0.001 to 20 mg/kg, preferably about 0.01 to 5 mg/kg, of body weight to achieve effective results, and in the case of oral administration the dose is about 0.01 to 50 mg/kg, preferably 1 to 10 mg/kg, of bodyweight.

In spite of this, it may in some cases be necessary to depart from the amounts mentioned, namely depending on the

body weight or the type of administration routes, on individual behaviour towards the medicaments, the manner

of its formulation and the time or interval at which administration takes place. Thus in some cases it may be sufficient to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of the administration of relatively large amounts, it may be advisable to divide these into several individual doses over the course of the day.

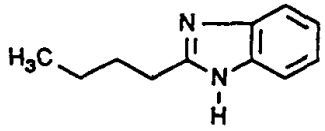
Solvent mixtures:

A	=	petroleum ether/ethyl acetate	1:1
B	=	petroleum ether/ethyl acetate	1:1.5
C	=	toluene/ethyl acetate	1:3
D	=	ethyl acetate	
E	=	petroleum ether/ethyl acetate	3:7
F	=	toluene/ethyl acetate	1:1
G	=	petroleum ether/ethyl acetate	1:3

Starting compounds

Example I

2-n-Butylbenzimidazole



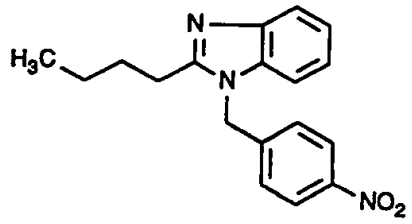
A mixture of 10.8 g (0.1 mol) of o-diaminobenzene, 10.9 ml (0.1 mol) of valeric acid and 100 ml of polyphosphoric acid is stirred at 120°C for 7 h. It is then added to 1.2 l of ice water, adjusted to pH 5 with NaOH (solid), treated with Na_2CO_3 until evolution of gas has ended and extracted three times with ethyl acetate. The combined organic phases are dried over Na_2SO_4, filtered and concentrated.

Yield: 15.8 g (91 mmol) 91 % of theory

R_f: 0.77 (ethyl acetate/methanol = 10:1)

Example II

p-[2-(n-Butyl-1H-benzimidazolyl)methyl]nitrobenzene



A solution of 34.9 g (0.2 mol) of 2-n-butylbenzimidazole in 250 ml of DMF is slowly added dropwise at 0°C under argon to a suspension of 6.0 g (0.2 mol) of NaH (80 %) in 200 ml of DMF. After stirring at 0°C for 10 min, a solution of 47.5 g (0.22 mol) of p-nitrobenzyl bromide in 250 ml of DMF is added dropwise, and the mixture is stirred for a further 2 h at 0°C and for 1 h at room temperature. It is then concentrated at 40°C, the residue is treated with ether and water, the mixture is shaken,

insoluble material is filtered off, the organic phase is separated off, the mixture is extracted with ether a further 2 times, and the combined organic phases are dried over Na_2SO_4, filtered and concentrated.

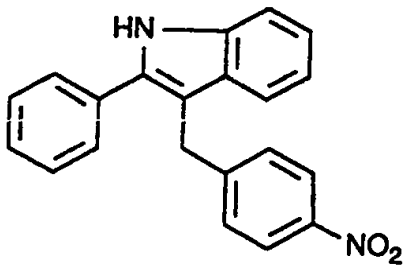
Crude yield: 78 g

R_f (product): 0.47 (toluene/ethyl acetate = 1:1)

The product is reacted further without purification.

Example III

p-[3-(2-Phenyl-1H-indolyl)methyl]nitrobenzene

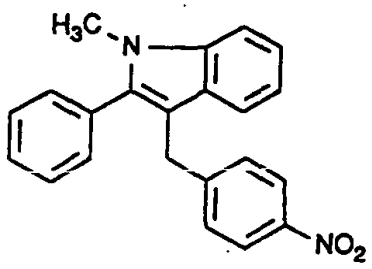


A solution of 5.8 g (30 mmol) of 2-phenylindole in 40 ml of DMF is added dropwise at -10°C to a suspension of 0.8 g (30 mmol) of NaH (80 %) in 30 ml of DMF and the mixture is stirred for 15 min. After adding a solution of 7.1 g (33 mmol) of p-nitrobenzyl bromide in 40 ml of DMF dropwise, the mixture is stirred for 1 h at -10°C and for 4 h at room temperature. It is then treated with 2 ml of glacial acetic acid/10 ml of H_2O and concentrated at 40°C. The residue is stirred with ether/water, insoluble material is filtered off, and the mixture is shaken and

separated. The aqueous phase is extracted a further 2 times with ether, and the combined organic phases are dried over Na_2SO_4, filtered, concentrated and chromatographed on silica gel 60 (petroleum ether/ether = 7:3).
Yield: 1.1 g (3.3 mmol) 11 % of theory.
R_f: 0.41 (petroleum ether/ether = 7:3)

Example IV

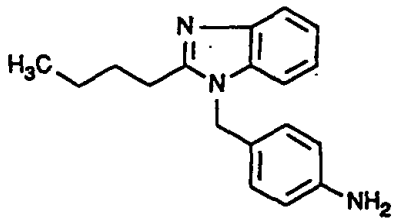
p-[3-(2-Phenyl-N-methylindolyl)methyl]nitrobenzene



A solution of 1.53 g (4.7 mmol) of p-[3-(2-phenyl-1H-indolyl)methyl]nitrobenzene in 15 ml of DMF is treated with 1.3 g (9.3 mmol) of K_2CO_3 and stirred for 15 min. After adding 0.3 ml (4.7 mmol) of iodomethane dropwise, the mixture is stirred for a further 2 days. Insoluble material is then filtered off, and the mixture is concentrated and chromatographed on silica gel 60 (petroleum ether/ethyl acetate = 10:1).
Yield: 1.3 g (3.7 mmol) 79 % of theory.
R_f = 0.64 (petroleum ether/ethyl acetate = 6:1)

Example V

p-[2-(n-Butyl-1H-benzimidazolyl)methyl]aniline



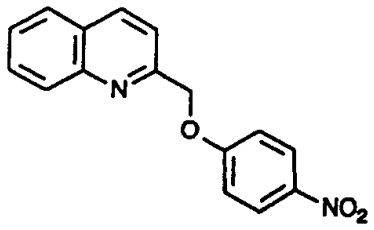
A solution of 72.8 g of the crude product from Example II in 500 ml of THF is treated, divided into 4 batches, with a total of 1 l of 1 N (1 mol) aqueous $TiCl_3$ solution and shaken for 1 h at 0.1 bar. 0.8 l of CH_2Cl_2 is then added. The mixture is brought to pH 9 using half-concentrated ammonia and insoluble material is filtered off. The precipitate is stirred again with 0.8 l of CH_2Cl_2 and filtered. The combined organic phases are concentrated to 500 ml, dried using the same volume of saturated Na_2SO_4, filtered and concentrated.

Yield: 42 g (0.15 mol) 75 % of theory over 2 steps

R_f = 0.34 (CH_2Cl_2/CH_3OH = 95:5)

Example VI

p-(2-Quinolinylmethylenoxy)-nitrobenzene



A solution of 13 g (0.33 mol) of NaOH in 400 ml of ethanol is treated with stirring at 80°C with 44 g (0.32 mol) of p-nitrophenol and the mixture is evaporated to dryness. The residue is taken up in DMF and added to a solution of 52 g (0.3 mol) of 2-chloromethylquinoline. After stirring at 120°C for 1 h, the mixture is diluted with 700 ml of H_2O, and the precipitate is filtered off, washed with water and dissolved in CH_2Cl_2. After extracting by shaking with water, the organic phase is dried and concentrated and the product is chromatographed on silica gel 60 using dichloromethane/ethyl acetate = 100:1.5.

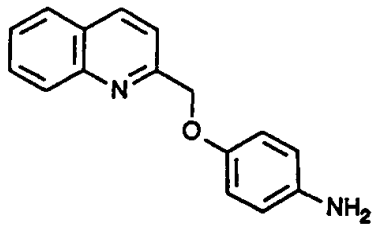
Yield: 74 g (0.26 mol) 88 % of theory

M.p. = 147°C

R_f = 0.44 (CH_2Cl_2)

Example VII

p-(2-Quinolinylmethylenoxy)-aniline



First 5 g (0.1 mol) of N_2H_4/H_2O, then, in small portions, Raney nickel in ethanol are added at 30°C with stirring to a suspension of 79 g (0.28 mol) of the compound from Example VI in 100 ml of methanol and 100 ml of THF. After the rise in temperature has ended, the mixture is refluxed for 1 h. It is then filtered and concentrated, the residue is taken up in CH_2Cl_2 and shaken with water, the organic phase is separated off, dried and concentrated, and the product is recrystallized from i-propyl ether/CH_2Cl_2.

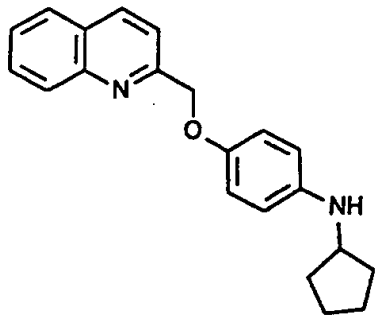
Yield: 69.2 g (0.276 mol) 98 % of theory

M.p.: 134°C

R_f = 0.39 (CH_2Cl_2/ethyl acetate = 7:3)

Example VIII

p-(2-Quinolinylmethylenoxy)-N-cyclopentylaniline



12.5 g (50 mmol) of the compound from Example VII are introduced under argon into 120 ml of THF at -78°C. After adding 31.3 ml of 1.6 N (50 mmol) n-BuLi dropwise in n-hexane, the mixture is subsequently stirred for 15 min, 7.5 g of cyclopentyl bromide are added, and the mixture is stirred for 15 min at -78°C, for 1 h at -20°C and for 2.5 days at room temperature. After diluting with THF, the mixture is shaken 3 times with $NaCl/H_2O$, and the combined aqueous phases are extracted once using THF. The combined organic phases are dried over Na_2SO_4, filtered and concentrated, and the product is purified by chromatography (silica gel 60, petroleum ether/ethyl acetate = 2:1).

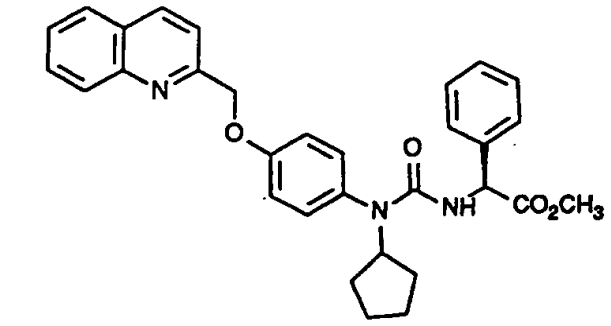
Yield: 5.4 g (17 mmol) 34 % of theory

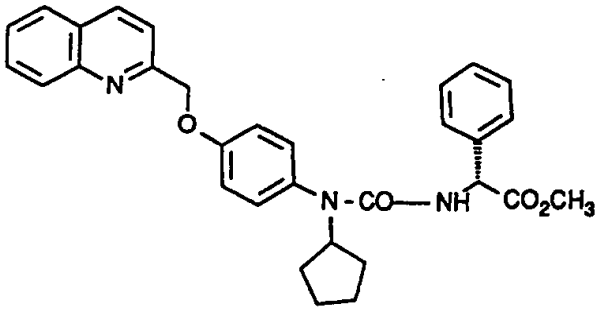
R_f = 0.53 (petroleum ether/ethyl acetate = 7:3)

Preparation examples

Example 1 and Example 2

N-[p-(2-Quinolinylmethylenoxy)phenyl]-N-cyclopentyl-N'-[S-(α-methoxycarbonyl)benzyl]urea





3.9 ml of 1.6 N (6.3 mmol) of n-BuLi in n-hexane are added dropwise with stirring at -78°C under argon to a solution of 2.0 g (6.3 mmol) of the compound from Example VIII in 25 ml of THF. After 15 min, a solution of 3.4 g (17 mmol) of methyl L-(2-isocyanato)phenylacetate

(prepared according to standard methods) is added dropwise via a dropping funnel cooled to -78°C. The mixture is stirred for 30 min at -40°C, in the next 30 min at -15°C and finally for 1.5 h at room temperature. It is then added to saturated NH_4Cl solution, extracted twice with ethyl acetate, the extracts are combined, dried, filtered and concentrated, and the residue is chromatographed (silica gel 60, ethyl acetate/petroleum ether = 1:1).

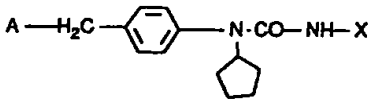
Yield: 1.8 g (3.5 mmol) 56 % of theory (Example 1)

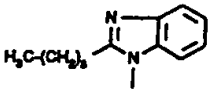
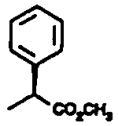
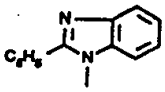
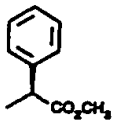
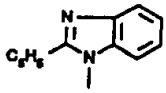
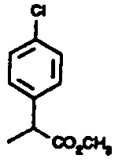
R_f = 0.68 (petroleum ether/ethyl acetate = 1:1) (Example 1)

R_f = 0.68 (A) (Example 2)

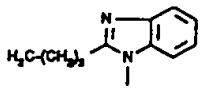
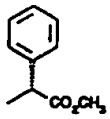
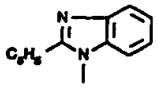
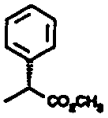
The compounds shown in Table 1 are prepared in analogy to the procedure of Examples 1 and 2:

Table 1:



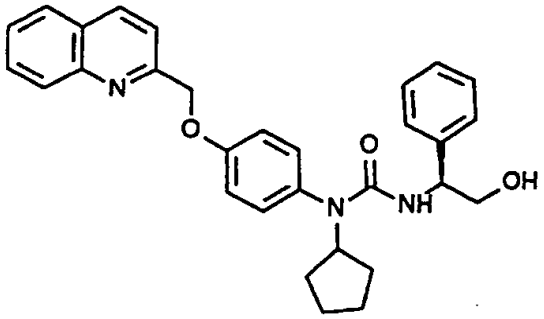
Ex. No	A	X	R_f (LM)
3			0.44 (A)
4			0.46 (A)
5			0.43 (A)

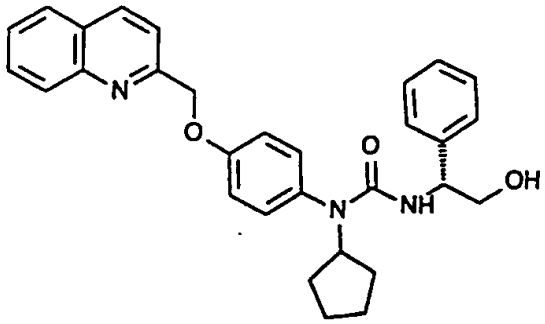
Continuation of Table 1

Ex. No	A	X	R_f (LM)
6			0.50 (B)
7			0.69 (E)

Example 8 and Example 9

N-[p-(2-Quinolinylmethylenoxy)-phenyl]-N-cyclopentyl-N'-[S-α-hydroxymethyl)benzyl]urea





A solution of 0.5 g (0.98 mmol) of the compound from Example 1 in 6 ml of THF is added under argon at room temperature to a solution of 2.6 ml of 1 N (2.6 mmol in THF) $LiAlH_4$ in 4 ml of THF and the mixture is stirred for 1 h. It is then slowly poured into 60 ml of ice water, adjusted to pH 5 with acetic acid and extracted three times with ethyl acetate, and the combined organic phases are dried over Na_2SO_4 filtered and concentrated. The product is purified on silica gel 60 (toluene/ethyl acetate = 1:2).

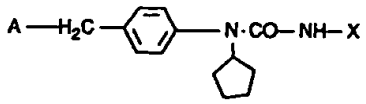
Yield: 120 mg (25 mmol) 25 % of theory (Example 8)

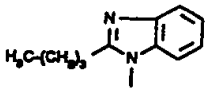
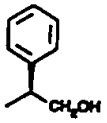
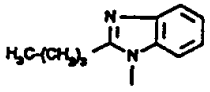
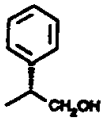
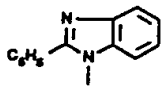
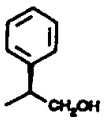
R_f = 0.49 (toluene/ethyl acetate = 1:3) (Example 8)

R_f = 0.49 (C) (Example 9)

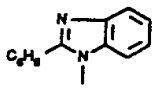
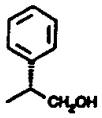
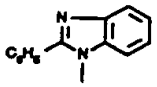
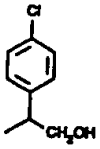
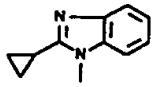
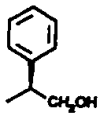
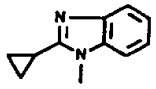
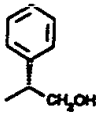
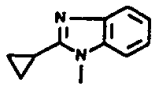
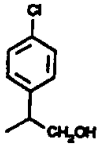
The compounds shown in Table 2 are prepared in analogy to the procedure of Examples 8 and 9:

Table 2

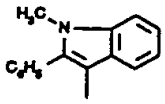
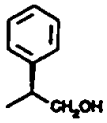
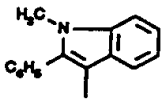
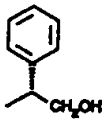
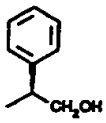


Ex. No	A	X	R_f (LM)
10			0.30 (C)
11			0.30 (C)
12			0.38 (C)

Continuation of Table 2

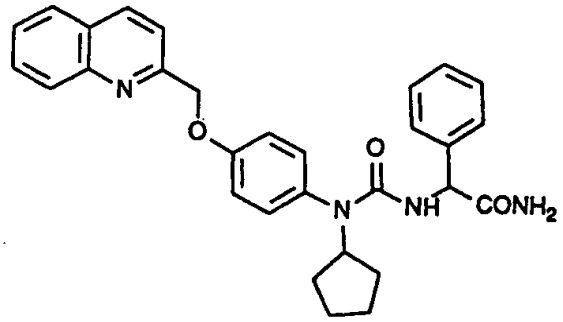
Ex. No	A	X	R_f (LM)
13			0.14 (F)
14			0.33 (C)
15			0.23 (D)
16			0.23 (D)
17			0.17 (D)

Continuation of Table 2

Ex. No	A	X	R_f (LM)
18			0.33 (A)
19			0.33 (A)
20	H		0.26 (F)

Example 21

N-[p-(2-Quinolinylmethylenoxy)phenyl]-N-cyclopentyl-N'-[S-(2-phenyl) acetamido]urea



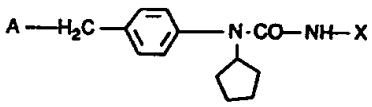
A saturated solution of ammonia in 25 ml of methanol is added to a solution of 0.5 g (0.98 mmol) of the compound from Example 1 in 6 ml of methanol and the mixture is stirred for 2 days at room temperature. After concentrating, the product is purified on silica gel 60 (ethyl acetate/petroleum ether = 7:3).

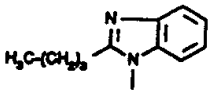
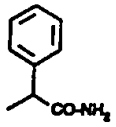
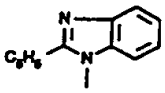
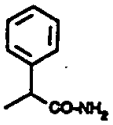
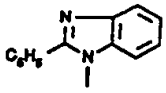
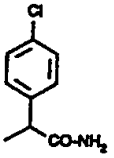
Yield: 0.3 g (0.61 mmol) 62 % of theory

R_f = 0.35 (petroleum ether/ethyl acetate = 3:7)

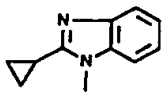
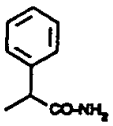
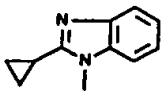
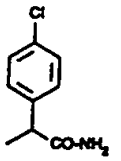
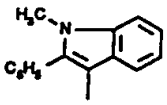
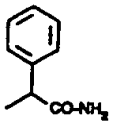
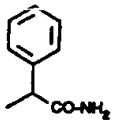
The compounds shown in Table 3 are prepared in analogy to the procedure of Example 21:

Table 3



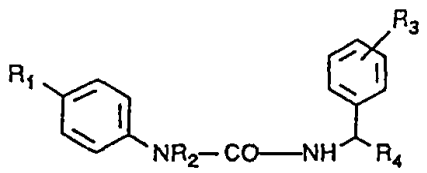
Ex. No	A	X	R_f (LM)
22			0,58 (D)
23			0.41 (D)
24			0.38 (C)

Continuation of Table 3

Ex. No	A	X	R_f (LM)
25			0.26 (D)
26			0.18 (D)
27			0.63 (G)
28	H		0.17 (F)

Patent claims

1. Substituted arylureas of the general formula (I)



(I)

in which

R^1 represents a radical of the formula $-CH_2-A$ or $-O-CH_2-D$,

in which

A and D are identical or different and denote hydrogen or a 5- to 7-membered, saturated or unsaturated heterocycle having up to 3 nitrogen atoms, to which a phenyl or pyridyl ring is optionally fuzed, and where in the case of an N-containing ring the bonding to the methylene group can also take place via the nitrogen function, and where the cycles are optionally substituted up to 3 times by identical or different straight-chain or branched alkyl, alkoxy or alkoxycarbonyl in each case having up to

8 carbon atoms, cycloalkyl having 3 to 6 carbon atoms, phenyl, hydroxyl, carboxyl or halogen,

R^2 represents cycloalkyl having 3 to 7 carbon atoms or straight-chain or branched alkyl having up to 8 carbon atoms,

R^3 represents hydrogen or halogen,

and

R^4 represents carboxyl or straight-chain or branched alkoxycarbonyl having up to 8 carbon atoms, or
represents straight-chain or branched alkyl having up to 6 carbon atoms, which is substituted by hydroxyl, or
represents a group of the formula $-CO-NR^5R^6$,

in which

R^5 and R^6 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,

and their salts.

2. Substituted arylureas according to Claim 1

in which

R^1 represents a radical of the formula $-CH_2-A$ or $-O-CH_2-D$,

in which

A and D are identical or different and denote hydrogen, benzimidazolyl, 3H-imidazopyridyl, 3-indolyl or 2-quinolinyl, which are optionally substituted up to 2 times both in the phenyl and in the heterocyclic radical by identical or different straight-chain or branched alkyl, alkoxy or alkoxycarbonyl in each case having up to 6 carbon atoms, cyclopropyl, cyclopentyl, cyclohexyl, hydroxyl, phenyl, carboxyl, fluorine, chlorine or bromine,

R^2 represents cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl, or
represents straight-chain or branched alkyl having up to 6 carbon atoms,

R^3 represents hydrogen, fluorine, chlorine or bromine,

and

R^4 represents carboxyl or straight-chain or branched alkoxycarbonyl having up to 6 carbon atoms, or
represents straight-chain or branched alkyl having up to 4 carbon atoms, which is substituted by hydroxyl, or
represents a group of the formula $-CO-NR^5R^6$,

in which

R^5 and R^6 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms

and their salts.

3. Substituted arylureas according to Claim 1

in which

R^1 represents a radical of the formula $-CH_2-A$ or $-O-CH_2-D$,

in which

A and D are identical or different and denote hydrogen, benzimidazolyl, 3H-imidazopyridyl, 3-indolyl or 2-quinolinyl, which are optionally substituted up to 2 times both in the phenyl

and in the heterocyclic radical by identical or different straight-chain or branched alkyl, alkoxy or alkoxycarbonyl in each case having up to 5 carbon atoms, cyclopropyl, cyclopentyl, cyclohexyl, hydroxyl, phenyl or carboxyl,

R^2 represents cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl, or
represents straight-chain or branched alkyl having up to 4 carbon atoms,

R^3 represents hydrogen, fluorine, chlorine or bromine,

and

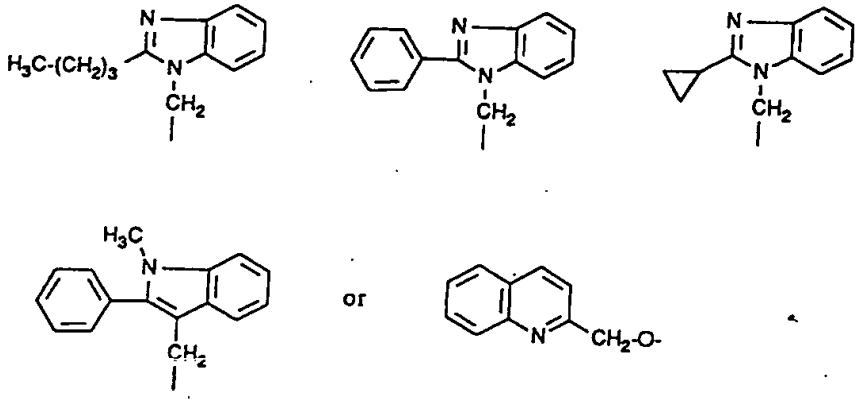
R^4 represents carboxyl or straight-chain or branched alkoxycarbonyl having up to 3 carbon atoms, or
represents straight-chain or branched alkyl having up to 3 carbon atoms, which is substituted by hydroxyl, or
represents a group of the formula $-CO-NR^5R^6$,

in which

R^5 and R^6 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

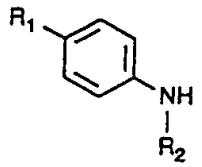
and their salts.

4. Substituted arylureas according to claim 1, in which R^1 represents hydrogen or the radical of the formula



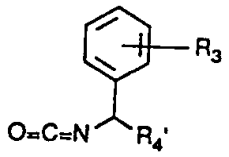
5. Substituted arylureas according to claims 1 to 4 for therapeutic use.

6. A process for preparing an arylurea of formula (I) as defined in claim 1, or a salt thereof, which process comprises reacting a compound of the general formula (IV)



(IV)

in which R^1 and R^2 are as defined in claim 1, with a compound of the general formula (V)



(V)

in which R^3 is as defined in claim 1 and $R^{4'}$ represents straight-chain or branched alkoxycarbonyl having up to 8 carbon atoms, followed, if required, by:

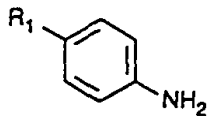
(i) hydrolysis of the alkoxycarbonyl group $R^{4'}$ to obtain a compound of the general formula (I) in which R^4 is a carboxyl group; or

(ii) reduction of the alkoxycarbonyl group $R^{4'}$ to obtain a compound of the general formula (I) in which R^4 is an alkyl group substituted by hydroxy; or

(iii) reacting a compound of the general formula (I) in which R^4 is a carboxyl group or an alkoxycarbonyl group, if required after activation of the carboxyl function with ammonia or an amine of formula R^5R^6NH in which R^5 and R^6 are as defined in claim 1 to obtain a compound of the general formula (I) in which R^4 represents a group of the formula $-CO-NR^5R^6$; and, if required,

(iv) converting an obtained compound of the general formula (I) into a salt thereof.

7. A process according to claim 6, wherein the compound of the general formula (IV) is obtained by reacting a compound of the general formula (II)



(II)

in which R^1 is as defined in claim 6, with a compound of the general formula (III)

$$R^2\text{-}L \qquad \text{(III)}$$

in which R^2 is as defined in claim 6 and L represents halogen.

8. A medicament containing substituted arylurea according to any one of claims 1 to 4, or a physiologically acceptable salt thereof, together with a suitable diluent or carrier.

9. A medicament according to claim 8, for inhibiting the proliferation of smooth muscle cells.

10. A medicament according to claim 8, for the treatment of arteriosclerosis and restenosis.

11. Use of a substituted arylurea according to any one of claims 1 to 4, or a physiologically acceptable salt thereof, for inhibiting the proliferation of smooth muscle cells or for the treatment of arteriosclerosis and restenosis.

12. A process for preparing a medicament for inhibiting the proliferation of smooth muscle cells or for the treatment of arteriosclerosis and restenosis, which process comprises admixing a substituted arylurea according to any one of claims 1 to 4, or a physiologically acceptable salt thereof, with a

suitable diluent or carrier.

13. A commercial package containing, as active pharmaceutical ingredient, a substituted arylurea according to any one of claims 1 to 4, or a physiologically acceptable salt thereof, together with instructions for its use for inhibiting proliferation of smooth muscle cells or for the treatment of arteriosclerosis and restenosis.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA

PATENT AGENTS

Substituted arylureas

A b s t r a c t

Substituted arylureas can be prepared by reaction of appropriately substituted amines with substituted aryl isocyanates. The substituted arylureas are suitable as active compounds in medicaments, in particular for the inhibition of the proliferation of smooth muscle cells.